Dual diuretic therapy for hypertension in advanced chronic kidney disease

Abdul Wahab Mirza[1], Zainab Jawad[2]

Hypertension affects approximately 85% of individuals with advanced chronic kidney disease (glomerular filtration rate < 30 ml/min), primarily due to increased volume load.[1] At this stage, kidneys lose their ability to achieve the desired fractional excretion for sodium (FeNa), thus predisposing the patient to hypertension. Loop diuretics, such as furosemide, are the mainstream drugs for patients of hypertension with chronic kidney disease. They block the Na-K-Cl channels thus increasing the FeNa. However, there are two important shortcomings of chronic loop diuretic use. Prolonged use of loop diuretics often leads to adaptive hypertrophic changes in the distal nephron, facilitating sodium reabsorption at this site and contributing to loop diuretic resistance. Additionally, the short duration of action of loop diuretics can result in incomplete control of fluid overload and blood pressure.[2] Also, a sudden discontinuation of loop diuretic causes reflex hypertension due to compensatory sodium absorption.

Traditionally, thiazide diuretics were considered ineffective in advanced CKD, particularly when GFR falls below 30 mL/min, due to their perceived inability to induce significant natriuresis or reduce blood pressure.

Table 1: (Comparison of three studies comparing the effects of mono vs combined therapy. Combination therapy consistently shows superior systolic and diastolic BP reductions, and better volume control, compared to monotherapy)

Study	Therapy Type	Systolic BP reduction (mmHg)	Diastolic BP reduction (mmHg)	Extracellular water Reduction(L)	eGFR decline (ml/min/1.73m^2)
Khan et al. (2017)[5]	Combination (Furosemide + HCTZ)	-19.3	-6.6	-3.8	-3.4
	Monotherapy (Furosemide)	-10.6	-3.4	-2.1	-2.8
	Monotherapy (HCTZ)	-3.7	Not significant	-1.5	-1.6
Dussol et al. (2011)[4]	Combination (Furosemide + HCTZ	-15	Not specified	Significant increase in Na+ and Cl- excretion	-7
	Monotherapy (Furosemide)	-8	Not specified	Moderate Na+ and Cl- excretion increase	-4
	Monotherapy (HCTZ)	-8	Not specified	Moderate Na+ and Cl- excretion increase	-4
Solis-Jimenez et al. (2022)[3]	Combination (Bumetanide + Chlorthalidone)	-26.1	-13.5	-3.05	Not specified
	Monotherapy (Bumetanide + Placebo)	-10	-3.4	-0.15	Not specified

[1] Second Year MBBS Student, Allama Iqbal Medical College, Lahore, Pakistan.
[2]Fourth Year MBBS Student, Foundation University Medical College, Islamabad, Pakistan.
Correspondence: Abdul Wahab Mirza.
Email: abdulwahabmirza916@gmail.com
ORCID ID: 0009-0009-5239-6987

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Current KDIGO guidelines support this view, recommending loop diuretics as the primary choice. However, recent evidence challenges these assumptions.[3] Emerging studies demonstrate that thiazide diuretics, including hydrochlorothiazide and chlorthalidone, retain their ability to promote sodium excretion and lower blood pressure in advanced CKD patients. Moreover, thiazide diuretics are potassium

wasters and this is beneficial in patients of CKD as they are hyperkalaemic so it also cures hyperkalaemia. These findings state the clinical impact of thiazide diuretics.[4]

Moreover, we want to address the achievement of remarkable results with the use of combined thiazide and loop diuretics for these patients. This combination addresses the limitations of loop diuretics by blocking sodium reabsorption at multiple segments of the nephron, leading to enhanced sodium and chloride excretion, better blood pressure control, and sustained diuretic efficacy. Studies have reported significant improvements in volume control and reductions in blood pressure with the co-administration of agents like furosemide and hydrochlorothiazide or chlorthalidone. However, this approach requires cautious application due to risks of adverse effects, including hypotension and electrolyte disturbances. This combination should be limited to patients with advanced CKD, who are unresponsive to monotherapy.[5] These findings suggest a shift in the treatment paradigm for hypertension in advanced CKD, advocating for the reconsideration of thiazides and their combination with loop diuretics in late-stage disease management.

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AWM & ZJ: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.